

# One year in review 2019: novelties in the treatment of rheumatoid arthritis

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## ABSTRACT

*The current treatment approach in rheumatoid arthritis (RA) follows a stepwise management, starting from early introduction of conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs), moving to biological (b) DMARDs and targeted synthetic (ts) DMARDs. In the last few years, new drugs with different mechanisms of action have demonstrated their efficacy in treating such a disabling condition, and their approval, along with other more “experienced” treatments, has established their effectiveness on disease activity, damage accrual prevention, patients’ quality of life improvement, confirming their safety profile. Moreover, new molecular pathways are under investigation as potential targets of new advanced therapies. Clinicians’ capability of stratifying treatment strategies and decisions has improved, with several new tools for the optimisation of long-term management of RA; however, many patients are refractory to the available drugs. Finally, as RA is a systemic disease, the knowledge in multi-systemic complications of the disease has grown, as well as the possibility in improving extra-articular manifestations of the disease, although certain drugs have potentially relevant non-articular effects, which need to be monitored. This narrative review summarises the most relevant studies published over the last year in the field of treatment of RA, with the major aim to let clinicians and researchers reflect on “what is new”, “what is effective” and “what is safe”.*

## Introduction

Current therapeutic approaches in rheumatoid arthritis (RA) aim at reaching early and persistent low disease activity or remission, with the stepwise adoption of different available drugs,

starting from conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs), moving to biological (b) DMARDs and targeted synthetic (ts) DMARDs. Different sets of international recommendations suggest the best treatment strategy, however still a high proportion of patients is refractory to first-line treatment adopted. Moreover, following the progressively increasing number of new drugs, clinicians reinforce their questions regarding the decision of the suitable drug to use at single patient level. In the last year, scientific societies have made many efforts to improve knowledge regarding new drugs able to interfere with interleukin (IL)-6-dependent inflammation and its downstream signalling. Moreover, new long-term efficacy and safety data are available regarding tsDMARDs tofacitinib and baricitinib, while the selective Janus Kinase (JAK)-1 inhibitor upadacitinib has demonstrated its efficacy and safety in RA. Possibilities of interfering with B-cells production of systemic mediators, with T-cells co-stimulation and with tumour necrosis factor (TNF)-alpha-dependent joint inflammation have been explored in translational and clinical researches, with new important insights even for “experienced” drugs, while the huge availability of biosimilars is still under the lens of researchers, in particular for safety concerns and strategies comparisons. New drugs are in phase of development, including novel targeted biological and synthetic therapies. The amount of results from pre-clinical, clinical, post-marketing studies of different cs-, b- and ts-DMARDs, as well as important conclusions obtained from meta-analysis, have increased the knowledge regarding their efficacy, damage accrual prevention and impact on patient’s perceptions of the disease. Some interesting studies clarify impor-

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tant clues regarding the best treatment strategy in particular settings and conditions, while the search for personalised medicine is still ongoing. Finally, given the systemic nature of RA inflammation, new evidence are available regarding the possibility of reducing the systemic burden of the disease, with particular focus on cardiovascular (CV) and infectious risks.

Starting from the last annual paper on this topic (1), this review aims at resuming the most relevant studies published over the last year on the management of RA. This review is a part of an editorial initiative of *Clinical and Experimental Rheumatology* focusing on the relevant novelties on rheumatic diseases published in the last year (1–11). In this review, particular focus is given to new efficacy and safety aspects of the vast armamentarium of drugs available, with different interference on key drivers of inflammation, as well as to different treatment strategies suitable to be explored in particular time-points of the illness, and to systemic consequences of the chronic disease.

### Targeting IL-6 and its downstream signalling

In the last year, research studies have confirmed the relevance of interfering with IL-6-driven inflammation on the management of RA.

Sirukumab (SRK) is a fully human monoclonal antibody (mAb) that binds to IL-6 with high affinity and specificity, preventing IL-6 from binding to membrane and soluble forms of the IL-6 receptors (IL-6R). Two doses regimens in subcutaneous (SC) administration were chosen for the phase III pivotal studies in the treatment of RA: 50 mg every 4 weeks and 100 mg every 2 weeks. The SIRROUND-H trial (12), a randomised, double-blind, parallel-group, phase III study, compared the efficacy of SRK monotherapy (186 patients 50 mg/4 weeks; 187 patients 100 mg/2 weeks) with adalimumab (ADA) monotherapy (186 patients) over 52 weeks, in patients with active RA who had inadequate response or intolerance to methotrexate (MTX). The first primary endpoint of the study was improvement from baseline in Disease

Activity Score (DAS)28 - erythrocyte sedimentation rate (ESR). At week 24, DAS28-ESR improvement was significantly higher for SRK 100 mg compared with ADA (mean change in DAS28: -2.96 vs. -2.19,  $p < 0.001$ ) and for SRK 50 mg (mean change in DAS28: -2.58 vs. -2.19,  $p < 0.013$ ). Differences in secondary endpoints (American College of Rheumatology (ACR)50 response rate, Clinical Disease Activity index (CDAI), Health Assessment Questionnaire Disability Index (HAQ-DI) scores, meaningful variation on the Short-Form Health Survey 36 (SF-36) and in Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-Fatigue) scores) were not significantly different in the two groups. Regarding safety profile, overall incidences of treatment-emergent adverse reaction (TEAEs) for patients randomised to ADA, SRK 50 mg/4 weeks and SRK 100mg/2 weeks were respectively 69.9% (130/186), 74.7% (139/186), and 71.7% (134/187). Among patients receiving ADA, SRK 50mg and SRK 100mg, the rate of serious infections was 2.2% (4/186), 7.5% (14/186), and 2.7% (5/187) respectively. At present, Food and Drug Administration (FDA) and European Medicines Agency (EMA) have not accepted SRK for approval in the treatment of RA, and the company, given the need for additional clinical data and the fact that other treatments blocking the action of IL-6 are available, has strategically decided to withdraw from the application and to terminate the development programme.

Sarilumab (SAR) is a human immunoglobulin (Ig)G1 that binds specifically to both soluble and membrane-bound IL-6R, approved by the FDA and EMA for the treatment of RA in 2017. Recently, in an open label extension of the MOBILITY trial (a phase III trial comparing SAR 150 mg/2 weeks, SAR 200mg/2 weeks, and placebo in active MTX-insufficient responders (IR) RA patients), Genovese *et al.* (13) evaluated safety and efficacy after 2 years of therapy in 776 patients, all receiving SAR 200 mg/2 weeks, irrespective of previous treatment randomisation in the blinded study. Rates of DAS28-C-reactive protein (CRP) remission, CDAI

and Simple Disease Activity Index (SDAI) remission achievement at week 104 were similar, independently of initial allocation, as well as changes in HAQ-DI score. Two-year radiographic data were available for 800 patients, with patients initially randomised to SAR 200mg/2 weeks displaying the most favourable radiographic outcome compared to those initially randomised to placebo or SAR 150mg/2 weeks. Despite the limitation of an open-label extension study, in which only clinical responders proceed after completion of the double-blinded part, safety and efficacy outcomes of SAR plus MTX were comparable with other IL-6R blockers studies. The efficacy of SAR was also assessed on patient-reported outcomes (PROs), analysing the MONARCH trial (14), another phase III randomised controlled trial (RCT) comparing SAR monotherapy (184 patients) versus ADA monotherapy (185 patients) in RA patients intolerant or IR to MTX. SAR was significantly superior to ADA according to a number of PROs at week 24, including HAQ-DI, Visual Analogical Score (VAS) pain, Patient Global Assessment (PtGA), SF-36 Physical Component Summary (PCS), morning stiffness VAS and Rheumatoid Arthritis Impact of Disease (RAID).

Tocilizumab (TCZ) is the first mAb directed against IL-6R approved for the treatment of moderate and severe RA. After approximately 10 years of clinical experience with this drug, there is still a huge debate regarding the best treatment strategy to adopt after the failure of a first TNF-alpha inhibitor (TNFi). The possibility of switching to another TNFi (plus MTX) has been compared with swapping to TCZ monotherapy in the CORRONA register (15). 301 patients who initiated TCZ monotherapy (96% receiving drug intravenously - IV) and 702 who switched to another TNFi plus MTX were identified. Evaluating CDAI changes at 6 months (primary outcome), no significant difference between the two groups was demonstrated, regardless of MTX dosages in the TNFis group. Analogous results were found in the modified ACR (mACR)20 response criteria, mACR50 and HAQ-DI.

With different IL-6-directed agents investigated in RCTs, Bae *et al.* (16) have performed a network meta-analysis of 14 RCTs comparing the efficacy and tolerability of TCZ, SAR, and SRK in patients with active RA and inadequate response to MTX or TNFis. Among 6 RCTs involving TCZ, 3 SAR, and 5 SRK, a total of 9,753 patients met inclusion criteria. For the network meta-analysis, the authors adopted a Bayesian random-effect Model, while a Markov chain Monte Carlo method was used to obtain the pooled effect sizes. All bDMARDs achieved a significant ACR50 response compared with placebo. The best treatment for achieving ACR50 was TCZ 8 mg plus MTX (surface under the cumulative ranking curve (SUCRA) 0.9269), immediately followed by TCZ monotherapy, compared to other IL-6-directed drugs in monotherapy or in combination with MTX. No significant differences were observed in withdrawals due to AEs among different combination therapies with MTX (TCZ 8mg/kg, SRK 100mg, SAR 200mg), which suggest comparable tolerability among the three drugs, while bDMARDs monotherapies were associated with more discontinuations due to AEs.

Dose reduction of bDMARDs after achievement of a stable remission or LDA, as suggested by international recommendations, is another crucial aspect of the treatment of RA, and in particular of that with IL-6R inhibitors. Saiki and co-workers (17) have explored this strategy in a retrospective analysis, investigating the efficacy and safety of extending the interval between IV administration of TCZ from 4 to 6 weeks. Among 125 patients identified, 78 (69%) maintained LDA (based on DAS28-CRP definition) after the extension of the interval for more than 2 years. Contrariwise, 44 patients could not maintain LDA after spacing the infusions and returned to the every-4-week administration, with 42 of them reobtaining LDA. Spacing of doses is considered relatively safe, as a significant decrease in the rate of SAEs and common AEs was observed in the group receiving spaced infusions, with lower values of total cholesterol, tri-

glycerides and higher platelets (PLTs) count. Another possibility for reducing overall dosages of TCZ is drug withdrawal. Kaneko *et al.* (18) have evaluated, in an open label study extension of the SURPRISE study, the possibility of interruption of IV TCZ therapy (IV 8mg/kg every 4 weeks) in patients achieving remission. The SURPRISE was a 2-year open-label, multicentre, Japanese RCT that evaluated the efficacy and safety profile of adding TCZ to MTX (ADD-ON strategy) *versus* switching from MTX to TCZ (SWITCH strategy) after MTX failure. In this extension of the SURPRISE, 102 patients who achieved remission in these two groups after 52 weeks of therapy, stopped TCZ and were observed for other 52 weeks (51 in ADD-ON group continued MTX, 54 in the SWITCH arm were csDMARDs-free). Maintained remission at 52 weeks after TCZ discontinuation was similarly low in both groups (24.4% in ADD-ON *vs.* 14.3% in SWITCH,  $p=0.29$ ). Rates of maintenance of LDA in TCZ free patients were significantly higher in the ADD-ON group compared to the SWITCH one (55.1 *vs.* 26.6,  $p=0.005$ ). Overall, the restart of TCZ re-induced remission in 91.3% of patients and its efficacy was independent of concomitant MTX. These results suggest that stopping TCZ could be possible if stable remission is gained, in particular if patients continue their MTX co-therapy.

The issue of the role of concomitant csDMARDs treatment in combination with TCZ was explored in other relevant studies. In fact, another strategic option to consider, after achieving good clinical response with TCZ plus MTX, is to taper or suspend the concomitant csDMARD instead of the bDMARD. Edwards *et al.* (19) have investigated, in a randomised placebo-controlled non-inferiority study, the efficacy and safety of a tapering MTX dose *versus* a stable MTX dose in combination with IV TCZ, following achievement of an European League Against Rheumatism (EULAR) good/moderate remission, in patients with severe csDMARDs-IR RA. The first arm (n=136) was maintained with a stable dosage of MTX, the

second arm (n=136) tapered MTX up to withdrawal after 48 weeks of treatment. After 60 weeks, the proportion of patients maintaining good/moderate EULAR response was significantly higher in the tapering group compared with the stable dosage (76.5 *vs.* 65.4,  $p=0.036$ , odds ratio (OR) 1.803, 95% confidence interval (95%CI) 1.037–3.133), with similar safety outcomes. Also the COMP-ACT study (20), a randomised multicentre double-blind study, has evaluated the effects of MTX discontinuation in patients who achieved stable remission with a combination therapy of TCZ (SC 162 mg/every week or every other week) and MTX. 296 RA patients achieving DAS28-ESR remission at week 24 were randomised (1:1) to receive either TCZ plus placebo or TCZ plus MTX. At week 24, the DAS28-ESR response was similar in both groups, suggesting that discontinuing MTX co-therapy is another possible option in patients reaching disease remission under the effect of IL-6 inhibitor therapy, in particular in case of MTX intolerance.

#### Targeting JAK/STAT signalling

JAK / signal transducer and activator of transcription (STAT) – coupled receptors are crucial in response transduction following signals from different type I and type II cytokines, and different tsDMARDs are able to interfere with such signalling inhibiting one or more of the four JAK isotypes (JAK1, JAK2, JAK3, TYK2).

An international double-blind, placebo-controlled, phase III RCT (SELECT-NEXT)(21) has recently evaluated upadacitinib, a selective JAK1 inhibitor (JAKi), in 661 RA patients with inadequate response to csDMARDs. Patients received once-daily extended-release formulation of upadacitinib 15 mg or 30 mg or placebo as add-on to csDMARD for 12 weeks. Both dosages demonstrated a significant effectiveness, allowing to reach a DAS28-CRP score of 3.2 or less (at 12 weeks) in 48% of patients, in comparison with 17% of placebo-treated ( $p<0.0001$  for each dose *vs.* placebo). Significant positive results were also obtained for ACR20, CDAI and SDAI responses and for quality of life

assessment through HAQ-DI, FACIT-Fatigue and SF-36. Of note, improvements were significant for both doses by week 1. Most common reported adverse events were nausea and upper respiratory tract infections. The SELECT-BEYOND study (22) had the same design, primary endpoints and duration of SELECT-NEXT, and it assessed safety and efficacy of upadacitinib as add-on therapy to csDMARDs in almost 500 RA patients with inadequate response or intolerance to biologics. This phase III trial reported for both dosages significantly positive results with regard to efficacy at 12 weeks (DAS28-CRP  $\leq 3.2$  achieved by 43% and 42% of patients treated with upadacitinib 15 mg and 30 mg, respectively, *versus* 14% of the placebo-treated) and PROs. Once again, improvements were already significant after the first week. Unlike the other trial, SELECT-BEYOND reported a higher rate of serious infections, herpes zoster and adverse events leading to higher discontinuation rate in the 30 mg group compared with the 15 mg one.

PROs were recently also assessed from two phase IIb RCTs on filgotinib, another selective JAK1 inhibitor. Filgotinib, either as add-on therapy to MTX or as monotherapy, demonstrated rapid and sustained (from week 12 to 24) improvements in almost all PROs (measured using HAQ-DI, PtGA, FACIT-Fatigue and SF-36) compared with placebo (23).

Among the tsDMARDs licensed for the treatment of RA at the failure of first-line csDMARD treatment barrier, tofacitinib is a JAKi that preferentially inhibits JAK1 and JAK3. Several RCTs were published in the past years on the use of tofacitinib 5 or 10 mg twice daily in MTX-naïve RA patients (considering tofacitinib as monotherapy *vs.* MTX - ORAL Start) or in MTX-IR patients (considering tofacitinib either as monotherapy *versus* combination therapy with MTX (ORAL Scan), and with background MTX *versus* adalimumab plus MTX (ORAL Standard)). Two post-hoc analyses have been recently published on these RCTs, analysing the relationships between the achievement of good disease control already in the first months and the long-term out-

comes (24, 25). One of these post hoc analyses was conducted on ORAL Start and ORAL Standard for a total of 1,665 patients (24). It assessed the probability of achieving LDA or remission (defined using CDAI and DAS28 definitions) at months 6 and 12, given the failure to achieve threshold improvement from baseline (defined as change in CDAI  $\geq 6$  or DAS28-ESR  $\geq 1.2$ ) at months 1 and 3. This analysis has demonstrated that failure to achieve early improvements in disease activity with both doses of tofacitinib is predictive of low probability of achieving LDA and remission at months 6 and 12. Another post hoc analysis of ORAL Start and ORAL Scan including more than 1,400 patients (25) has showed that LDA or remission achievement at month 6 was associated with successful long-term outcomes, such as lower radiographic progression and higher improvement in HAQ-DI scores. Moreover, treatment with tofacitinib resulted in reduced radiographic progression even in patients with moderate or high disease activity when compared with MTX, suggesting a potential dissociation between inflammatory disease and joint damage in patients treated with tofacitinib.

During the past year, the safety of JAKis has been extensively revised. A meta-analysis of 6 RCTs has examined the safety of tofacitinib 5 and 10 mg twice daily as monotherapy or in combination with csDMARDs in a total of 3,881 RA patients (26). Safety profiles were generally similar between the two groups; however, although not statistically significant, incidence rates for some adverse events, like herpes zoster and infections requiring hospitalisation, were lower in patients receiving monotherapy *versus* combination therapy, irrespective of tofacitinib dose or glucocorticoid (GC) use. The safety of the two possible dosages of tofacitinib were also investigated by another meta-analysis (27), which pointed out that, after 3 and 6 months of treatment, similar risks of AEs, SAEs and adverse events leading to drug discontinuation were observed with tofacitinib 5 mg *versus* 10 mg (twice daily). The only significant difference was a reduction of haemoglobin (Hb) after 3 months

of treatment in patients taking 10 mg twice daily (relative risk (RR) 1.75, 95%CI 1.19–2.58).

Baricitinib is a selective JAK1 and JAK2 inhibitor, which is licensed for the second-line treatment of RA. A recent meta-analysis of 8 RCTs and one long-term extension study evaluated the safety profile of baricitinib in monotherapy or in combination with other csDMARDs, in 3,492 patients treated for a median of 2 years (maximum 5.5 years) (28). Except for a significantly higher rate of herpes zoster (incidence rate 3.2, 95%CI 2.8–3.7), in any case similar to that seen with other JAKis, baricitinib revealed an acceptable safety profile in the context of demonstrated efficacy. These findings were reaffirmed by another meta-analysis by Huang and colleagues (29), including 4 RCTs, which evaluated the safety of baricitinib 2 mg and 4 mg on a total of 959 patients. No significant differences in adverse drug events were observed between the two groups after 12 weeks of follow-up. After 24 weeks, a significantly higher risk of SAEs with baricitinib 4 mg was noticed (RR 1.84; 95%CI 1.02–3.30), whereas total AEs, discontinuation of drug due to AEs, malignancies, major cardiac events, infections including herpes zoster, and serious infections, were similar between the two doses.

Both ACR and EULAR guidelines suggest that, in patients achieving sustained remission with DMARD therapy, consideration should be given in attempting DMARD tapering, and this is applicable to tsDMARDs, too. A prospective study on 559 RA patients treated with baricitinib 4 mg for at least 15 months, who had achieved sustained disease control, namely LDA (CDAI  $\leq 10$ ) or remission (CDAI  $\leq 2.8$ ), has evaluated, after blinded randomisation, the effect of tapering baricitinib treatment to 2 mg for 48 weeks, compared with continuation of standard dosages (30). Most patients in both groups maintained disease control, however dose reduction resulted in small, but statistically significant, increase in disease activity at 12, 24 and 48 weeks, with earlier and more frequent relapses compared to 4 mg maintenance. However, the taper-

ing was associated with a numerically lower rate of non-serious infections. Even if maintenance of RA control was greater with 4 mg, most patients tapered to 2 mg daily could maintain LDA or remission and, for those who did not, disease control was recaptured after returning to 4 mg.

Real-world data generated during routine clinical practice outside the context of RCTs are essential in order to understand the efficacy and safety profile of JAKis in real-life, in comparison with other bDMARDs. A large retrospective study has recently analysed data from two databases regarding 21,832 RA patients undergoing tsDMARDs or bDMARDs treatment after the failure of first-line MTX. At the first year of follow-up, tofacitinib and non-TNFis appeared to have similar effectiveness rates, evaluated in terms of adherence, with no differences in DMARD switch or addition, GC joint injections and necessity of intensifying concomitant oral GC dosage (31). These large real-world data highlighted no relevant difference between tofacitinib and non-TNFis with respect to infections requiring hospitalisation, confirming the safety profile of JAKis even in real-life settings, with outcomes comparable to bDMARDs.

### Targeting B-cells

Rituximab (RTX) is an anti-CD20 chimeric monoclonal antibody that depletes B-cells population. B-cells have an important role in disease pathogenesis, contributing to antigen presentation, activation of T-cells and production of pro-inflammatory cytokines and autoantibodies. As a matter of fact, a randomised, double-blind, placebo-controlled clinical trial has proven that a single infusion of RTX 1000 mg significantly delayed the development of arthritis in 81 patients at risk of developing seropositive RA (32). In this study, subjects with serum positivity for both anti-citrullinated peptide antibodies (aCPA) and Rheumatoid Factor (RF), and high CRP levels or subclinical synovitis detected by ultrasonography (US) or Magnetic Resonance Imaging (MRI) were included. After a mean follow-up of 29 (0–54) months, no serious infections or SAEs related to the treatment

occurred, but only mild infusion-related symptoms, and patients treated with RTX developed arthritis with a mean delay of 12 months compared with those receiving placebo (hazard ratio (HR) 0.45 of developing arthritis at 12 months for RTX vs. placebo, 95%CI 0.154–1.322; at 18 months HR 0.48, 95%CI 0.19–1.19). The presence of serum anti-citrullinated  $\alpha$ -enolase peptide 1 (anti-CEP-1) at baseline (HR 3.71, 95%CI 1.51–9.18) positively correlated with the development of arthritis.

The long-term effectiveness of RTX in the treatment of overt RA has been confirmed in numbers of real-life studies. Data from the British Society for Rheumatology Biologics Register for RA (33) were used to investigate RTX persistence in treatment after 4 years of follow-up. In this analysis, among 1,629 starting RTX treatment as first- or second-line bDMARD treatment strategy, 60% of patients remained on treatment after 4 years, with high effectiveness and tolerability. RF-positive patients were confirmed as the most likely to persist after 4 years (HR for discontinuation in RF-negative patients 0.74, 95%CI 0.64–0.87). Most common reasons for RTX discontinuation were ineffectiveness, death and adverse events.

The development of hypo-gammaglobulinaemia and consequent infectious events are among potential risks of anti-CD20 treatments. A multicentre observational study in 134 RA patients receiving long-term treatment with RTX has showed that the risk of developing hypo-gammaglobulinaemia was higher with baseline gamma-globulin concentration lower than 8 g/L (34). This complication generally occurred after 64±23 months, and concomitant MTX therapy seems to be a protective factor. Again, patients who developed hypo-gammaglobulinaemia were more likely to experience severe infections (26.1% vs. 6.3%,  $p=0.033$ ).

Treatment with RTX could be proposed in RA patients after the failure of a single prior TNFi, and the risk of serious infections during the first year seems to be similar using either RTX or a second TNFi, as showed by a large national prospective observational study (35) from the British Society for

Rheumatology Biologics Register. This study has included 4,815 RA patients who switched to either a second TNFi-inhibitor or to RTX, after failing a first TNFi. Serious infections were defined as those requiring hospitalisation, intravenous antibiotics or resulting in death. The rate of serious infections was 59 and 66/1000 patient-years in TNFis and RTX groups, respectively, with an adjusted HR for the RTX group of 1.0 (95%CI 0.7–1.4). Among strategies developed in order to reduce the rate of serious infections, a possible option consists in the use of a reduced dose (<2000 mg) of RTX for further courses, following the initial recommended administration of 1000 mg in two subsequent infusions given 2 weeks apart. In an observational study on 1,278 RA patients from the AIR registry (36), the “reduced-dosages protocol” was associated with a significantly lower rate of serious infections. In particular, the incidence of serious infections was 2.2/100 patient-years in the reduced dose group versus 4.1/100 patient-years in the standard dose group ( $p=0.02$ ; adjusted HR 0.50; 95%CI 0.27–0.92). Treatment maintenance at 5 years was not affected by using reduced versus standard RTX dosages, suggesting a similar efficacy profile for both dose regimens, and highlighting a possible and feasible treatment strategy to adopt for long-term maintenance therapies.

As patent protection and data exclusivity for RTX expire, the availability of biosimilars has raised numbers of questions, in particular regarding safety concerns for switching from biological reference products (BRPs) to RTX-biosimilars. Recently, Cohen and colleagues (37) have performed an extension study on 185 TNFi-IR RA patients previously enrolled for more than 16 weeks in a pharmacokinetic similarity study of PF-05280586, a potential RTX biosimilar. After randomisation, patients previously treated with PF-05280586 continued the study medication, while patients who previously received RTX bio-originator were randomised at RTX bio-originator or switching to PF-05280586. The aim of this study was to evaluate pharmacokinetics, pharmacodynamics, immu-

nogenicity, safety, and tolerability of PF-05280586, with or without a single transition from RTX reference product. No significant differences between RTX reference product and PF-05280586 were found in terms of safety outcomes after 96 weeks of treatment, underlining that single transition from bio-originator to biosimilar is a feasible option for patients receiving CD20-inhibitors. Another RTX biosimilar is GP2013 and its clinical efficacy is comparable with RTX reference products. To evaluate the safety of switching from reference RTX to GP2013, a new international, multicentre, randomised, controlled study on 107 RTX-experienced RA patients was performed (on average, 4–5 courses of RTX treatment before the start of the study)(38). The primary objective of the study was to evaluate the safety of switching from reference RTX to RTX biosimilar GP2013 compared with treatment continuation with reference RTX. The safety profile was similar in both groups, in terms of infusion-related reactions (11.3% and 18.5%, respectively) and hyper-sensitivity (9.4% and 11.1%, respectively). Only one patient, who received reference RTX, developed antidrug antibodies, while no new occurrence of anti-drug antibodies was found in switchers. In conclusion, clinical trials investigating efficacy and safety of biosimilars are now pointing on different outcomes, and safety of switching from RTX bio-originator is considered among priorities in new biosimilars development. Real-life data are necessary in order to confirm this apparently safe profile.

#### Targeting T-cell co-stimulation

Abatacept (ABA) is a bDMARD that modulates co-stimulatory signals necessary for T-lymphocyte activation, inhibiting the binding of T-cells CD28 with Antigen Presenting Cells (APCs) CD80/CD86.

The possibility of a very early therapeutic intervention with both bDMARDs and csDMARDs might be associated with better treatment outcomes and with the possibility of exploring drug-free remission, as demonstrated by AVERT study. A recent *post hoc* analysis of this trial has investigated whether

symptoms duration could associate with the possibility of interrupting all RA therapies if an early and aggressive treatment strategy is adopted (39). The AVERT study included 351 active aCPA-positive early RA patients who were MTX-naïve or had received MTX for  $\leq 4$  weeks. 119 patients received ABA SC plus MTX, 116 ABA monotherapy and 116 MTX monotherapy for a 12-month treatment period, followed by a 12-month withdrawal period for all RA drugs in patients with DAS28-CRP  $< 3.2$ . Patients receiving ABA plus MTX showed a higher rate of remission at month 12 and of sustained drug-free remission at month 18 compared with those receiving MTX monotherapy. Earlier treatment with ABA plus MTX ( $\leq 3$  months) associated with the highest rate of drug-free remission (33.3% of ABA plus MTX-treated patients, 95%CI 17.9–48.7), compared with those with symptoms duration of 3–6 months (14.7%, 95%CI 5.0–31.1) and  $> 6$  months (10.2%, 95%CI 3.4–22.2). Another observation derived from the treatment of early MTX-naïve patients with combination therapy of ABA plus MTX refers to the possibility of obtaining conversion to aCPA/RF seronegative status. These results were highlighted by a *post hoc* analysis performed on the AGREE study (40). In this study, 509 MTX-naïve patients, with early erosive RA, positive for RF and/or aCPA antibodies, were randomised to receive ABA plus MTX or MTX monotherapy over a 12-month double-blind period, followed by open-label ABA plus MTX for additional 12 months. Combined treatment with ABA and MTX led to a decrease in both RF and aCPA titres over 6 and 12 months and conversion to RF and aCPA seronegative status, in 17.0–18.5% and 6.6–7.1% of patients, respectively. A higher proportion of patients who converted to aCPA seronegative status achieved DAS28-CRP and CDAI remission at month 6 compared to patients who were persistently aCPA-positive, and seroconversion associated with lower radiographic progression over 12 months, regardless of treatment.

SC formulation of ABA has demonstrated its efficacy in patients with inad-

equate response to MTX, and long-term efficacy and safety profiles are now available from RCTs. A recent study (41) has described 5-year safety, tolerability, and efficacy of ABA in 1,385 RA patients who were included in a phase IIIb, randomised, double-dummy, multinational trial (ACQUIRE study). After the initial 6-month double-blind period in which patients received IV or SC ABA plus MTX, 1,372 patients entered the open-label long-term extension, in which they received SC ABA (125 mg/week). 945 patients (68.8%) completed more than 5 years of treatment. As a whole, 97 (7.1%) patients discontinued treatment because of AEs; the incidence was stable over time, and no worsening of ABA safety or loss of efficacy were noticed with respect to the double-blinded part of the study.

Many investigations support the view that ABA has a consistent safety profile and durable efficacy for long-term management of RA, irrespective of the line of treatment. Data from a large administrative database from Lombardy region, Italy, on RA patients (n=4,656) who had at least one bDMARD delivery, has identified ABA as the bDMARD with the lowest risk of hospitalised infections (adjusted HR for ABA vs. etanercept (ETA) 0.29, 95%CI 0.10–0.82), suggesting that it should be considered for patients with higher baseline risk of infection. The risk was increased by concomitant therapy with GCs (HR 1.09 per mg/day, 95%CI 1.06–1.11), while it was reduced by MTX co-therapy (HR 0.72, 95%CI 0.52–0.99) (42). Moreover, CTLA-4 is an important target in animal models of lung inflammation, and a Spanish multicentre, non-controlled, open-label registry study of RA patients with RA-associated interstitial lung disease (ILD) has evaluated the capability of ABA to control this RA extra-articular manifestation (43). Among 63 patients, 55 (87.3%) had seropositive RA, and in 15 (23.8%) the development of ILD was deemed related to cs- or bDMARDs previous administration. ABA appeared beneficial in these patients, since, after a mean follow-up of  $9.4 \pm 3.2$  months, one-quarter of patients showed a clinical improvement in the Modified Medical

Research Council scale for dyspnoea and in carbon monoxide diffusivity, while two thirds remained stable. In addition, 36.4% (8/22) of the patients that repeated high-resolution computed tomography (HRCT) after 1 year for persistence of respiratory symptoms had improved HRCT features, while almost a half was stable.

#### **TNF-alpha inhibition: new insights from “experienced” drugs**

Therapy with TNFis is crucial in RA management, and this is the class of drugs with longer experience, given its availability for the treatment of RA since the early start of 2000s. There is still debate about the role of TNFis for first line treatment strategy in DMARDs-naïve RA patients, instead of using a csDMARD-based strategy, with further and gradual proceeding to bDMARDs or tsDMARDs, as recommended. Bortoluzzi *et al.* (44) have performed a systematic literature review (SLR) with the objective to explore the best therapeutic strategy in early RA treatment. In 6 studies (2013–2016), the authors have found no significant differences regarding clinical and functional benefits, as well as radiological progression, between DMARDs-naïve RA patients directly treated with TNFis compared to standard of care, suggesting no real rationale to perform an early aggressive TNFis treatment for patients with early DMARDs-naïve RA. The specific dosage of MTX when in combination with first-line TNFis is another matter of debate, in particular from patients' point of view. In a *post hoc* analysis of MUSICA trial, a randomised double-blind trial on 309 patients with active MTX-IR RA, the authors compared the effects of therapy with ADA in combination with MTX 7.5 mg/week (n=154) versus MTX 20 mg/week (n=155) (45). After 24 weeks, both groups had a statistically significant improvement on physical functions, quality of life, work impairment and activity, satisfaction with medication, sleep quality and sexual impairment, irrespective of MTX dosage. These findings suggest that ADA plus MTX combination therapy plays a primary role in achieving relevant

outcomes from a patient's perspective, and the effect of MTX co-medication is independent of its dosage.

However, in clinical practice, bDMARDs monotherapy is frequently observed. In a retrospective observational study from healthcare administrative databases on 4,478 patients with RA on first line approved bDMARD therapy (most treated with TNFis etanercept (ETA), ADA and INF), persistence in treatment was compared across different drugs when administered in monotherapy (46). Monotherapy with bDMARDs was associated with higher Charlson Comorbidity Index (CCI), lower GCs and non-steroidal anti-inflammatory drugs (NSAIDs) use. Combination therapy with csDMARDs had a lower risk of bDMARD failure (HR 0.79, 95%CI 0.72–0.88), and ETA monotherapy showed lower risk of failure compare to ADA (HR 1.28, 95%CI 1.03–1.59) and INF (HR 2.41, 95%CI, 1.85–3.15) monotherapies. Similarly to other studies, ETA was confirmed as first choice for first-line TNFis monotherapy compared to ADA and INF.

How to maintain therapy in patients with RA is still a debate, and the question regarding the possibility of stopping associated csDMARDs after reaching targets is appealing. Keystone *et al.* (47), in an open label extension of PREMIER study, have analysed 140 patients in long-term treatment after the completion of a 2-year double-blind study in which MTX-IR RA patients received ADA monotherapy, ADA plus MTX or MTX monotherapy. After reaching LDA at year 2, patients could receive ADA monotherapy for additional 8 months; open-label MTX up to 20 mg weekly could be added if investigators decided it. In this analysis, the authors have compared the group on open-label ADA monotherapy (n=84) with the group on ADA plus MTX (n=56) on clinical, functional and radiographic outcomes after 3 years. ADA monotherapy was effective in terms of disease activity, functional impairment, and radiographic progression and permitted to maintain LDA for other 3 years in more than 50% of patients, suggesting the possibility to stop concomitant MTX in (at least) selected patients.

Apart from suspending concomitant csDMARDs, numbers of patients experiencing long-term treatment with TNFis are now facing the opportunity to reduce TNFis dosage. Emery *et al.* (48) have recently analysed factors associated with successful tapering or suspension of ETA treatment in early RA patients. After a 52-week open-label study in which patients were treated with ETA plus MTX, patients in remission/LDA were randomised in three groups: reduced ETA (25 mg weekly) plus MTX (n=63), MTX monotherapy (n=65) and no RA therapy (n=65). In patients undergoing combination therapy, sustained remission was maintained in those who reached remission or LDA in a faster manner during the open-label phase, and in those with lower DAS28 values at the 52-week time-point. Brahe *et al.* (49) have evaluated a cohort of 141 patients with RA in persistent remission (DAS28-CRP $\leq$ 2.6 and no radiographic progression in the last year), monitoring patients for 2 years after tapering bDMARDs (mostly TNFis, 91%). The primary objective of the study was to evaluate bDMARDs tapering and its predictors of success. At the end of follow-up, 26/141 (18%) patients were receiving two third of a standard dose, 39/141 (28%) a half of the dose and 54/141 (38%) the full dose. Interestingly, the authors have found that 62% of patients maintained remission for two years. Radiographic progression was higher in patients in full dose therapy at 2 years in comparison to patients with tapered bDMARD dose, maybe due to persistent disease activity over-time. Predictors of effective bDMARD tapering were male gender,  $\leq$ 1 previous bDMARDs, low MRI inflammation and damage scores, negativity of RF.

Other than tapering, another possibility to reduce global intake of TNFis is to stop therapy after reaching the prefixed target. In the 12-month POET study, an open label trial on 817 RA patients in clinical persistent DAS28 remission or LDA for at least 6 months, enrolled subjects were randomised 2:1 to stopping or continuing TNFi therapy. A recent *post hoc* analysis aimed at investigating the possible impact of stopping TNFis on different PROs af-

ter 12 months of follow-up (50). After 3 months, PROs were worse in patients stopping TNFis than in those continuing them, in particular for health utility and pain domains. Moreover, patients restarting TNFis therapy within 6 months for articular flares, had no different impact on PROs at 12 months in comparison with patients who did not restart any treatment, suggesting that, from a patient's point of view, discontinuing TNFis is perceived as negative, and treatment restart does not recapture this negative feeling, at least in the short-term period. Another significant aspect to consider when facing TNFis discontinuation regards infections occurrence, and there is debate about the best treatment strategy to adopt after a recent serious infection. Subesinghe *et al.* (51) have studied the serious infections that happened in 1,583 patients on TNFis from the prospective British Society for Rheumatology Biologics Register, and evaluated re-occurrence of serious infections after 12 months in relation to different treatment strategies, namely stopping bDMARDs, re-starting the same bDMARD or swapping to another class of bDMARDs. Patients continuing TNFis (events 42.6% per annum, 95%CI 32.5–55.7%) or swapping to other bDMARDs (12.1% per annum, 95%CI 3.9–37.4%) had lower risks of recurrent infections compared to patients stopping the treatment. In particular, swapping to other mechanisms of action resulted in the lowest risk of new serious infections (adjusted HR 0.29, 95%CI 0.09–0.95), compared to TNFi continuation (HR 0.54, 95%CI 0.40–0.74). A better control of the disease is claimed as the most important explanation of such observations, but a careful evaluation at single patient level remains the gold standard in decisions making.

Regarding the complex topic of biosimilars, one of the most challenging points refers to safety and efficacy of switching from reference products to biosimilars, and this is true in particular for TNFis. In a randomised, double blind, phase III transition study, Smolen and co-workers (52) have tested the efficacy, safety and immunogenicity of SB2, an INF biosimilar, in 584 RA patients

with moderate to severe MTX-IR RA. Firstly, patients were randomised in two groups, one received INF BRP and the other its biosimilar SB2 from baseline to 54 weeks. At week 54, in a second re-randomisation, patients receiving INF bio-origimator shifted to SB2 (INF to SB2 group, n=94) or remained in INF-origimator (INF to INF group, n=101) up to week 70. Either efficacy and safety outcomes were similar in the two groups, as well as anti-drug autoantibodies development. With a similar study-design, Weinblatt and colleagues (53) have compared a switching strategy from ADA bio-origimator to ADA biosimilar SB5, with continuing ADA-BRP from 24 up to 52 weeks, following a first phase in which MTX-IR patients received ADA-BRP or SB5. 254 patients were randomised, of whom 129 continued treatment with ADA origimator and 125 switched to SB5, with similar efficacy and safety outcomes at 52 weeks in both groups. These studies confirm, in the context of RCTs, safety outcomes and efficacy maintenance after switching from ADA and ETA BRPs to their respective biosimilars.

Observational studies confirm these trends, with some exceptions given the alternative design and the 'real-life' perspective. In a Danish observational study from the DANBIO registry, safety and efficacy outcomes are now available after one year of mandatory transition from ETA-BRP to ETA biosimilar (SB4), in a cohort of 2,061 RA and Spondyloarthritis patients with stable disease activity during the 3-month period before study entrance (54). Switchers (n=1,621) were compared to non-switchers and to a historic cohort of ETA-BRP continuers. 12-month adjusted retention rates were higher in switchers (83%, 95%CI 79–87%) than in non-switchers (77%, 95%CI 72–82%), but both were lower than in the historic cohort (90%, 95%CI 88–92%), and in each group withdrawal rates were higher in patients not in remission before entering the study. Moreover, 7% of switchers came back to ETA-BRP, claiming for lack of efficacy, but main reason guiding back-switch was patient's global activity, suggesting the importance of patients related factors in

driving the outcomes of switching strategies. Even from the point of view of outpatient healthcare resources utilisation, switching from BRPs to biosimilars seems to impact in a slight manner, as demonstrated by Glintborg *et al.* (55) in the same DANBIO registry, focusing on the role of mandatory switching from INF origimator to INF-biosimilar CT-P13. The mean number of visits in the 6-month period before and after switching were respectively 3.89 and 3.95 ( $p=0.35$ ), with no clinically relevant necessity of increased medical care in patients during the 6-month period across the switching decision.

As a way of summarising, Feagan *et al.* (56) have performed a SLR on 70 published studies (13 RCTs, 53 observational) regarding switching from INF-BRP to INF-biosimilars, analysing safety, efficacy and immunogenicity in diverse autoimmune inflammatory diseases. In their analysis, the authors have concluded that there are no significant risks for one-time switch from origimator to biosimilar in terms of safety and efficacy, at least for INF (with few exceptions). Only one RCT (NOR-SWITCH), however, reported non-inferiority for switching *versus* continuing BRPs, while the others did not furnish equivalence comparisons, and, in the majority, switch occurred during on open-label extension phase of the trial, in the absence of statistical power to demonstrate non-inferiority or equivalence. Lack of control arms is claimed as one of the most relevant limitations in observational studies, as well as co-existence of subjects with different autoimmune diseases. However, published data are not sufficient to evaluate multiple switches between different biosimilars, and this theme should be assessed in the near future.

#### Other targeted therapies

During the last year, the potential benefits deriving from the inhibition of the IL-17 axis in the management of RA have been extensively investigated. A phase III placebo-controlled RCT has evaluated secukinumab (SEC), an IL-17A inhibitor approved for the treatment of spondyloarthritis and psoriasis for 24 weeks in 242 RA patients who



failed to respond to TNFis (57). None of the two dosages tested was found to be significantly superior to placebo, although confirming the well-known safety of secukinumab. Similarly, CNTO6785, a fully human monoclonal antibody targeting IL-17A, was evaluated in a phase II dose-ranging RCT in MTX-IR RA patients (58), randomised to receive different dosages of CNTO6785 or placebo every 4 weeks with background MTX. After 32 weeks the drug was well tolerated but did not demonstrate any clinical efficacy (or dose-response relationship) with respect to placebo. Another RCT (phase II) sought to evaluate the potentials of blocking simultaneously TNF-alpha and IL-17A pathways. Genovese and colleagues have assessed the safety and efficacy of ABT-122, a dual variable domain Ig capable to target both TNF-alpha and IL17A, in 222 MTX-IR RA patients (59), randomised to receive subcutaneous ABT-122 at different dosages or ADA. After 12 weeks of treatment, AEs were similar across all groups and the efficacy of any dosage of ABT-122 (primary endpoint ACR20 response) was found to be not significantly different from that of ADA; only ACR70 was significantly better in ABT-122-treated subjects *versus* ADA-treated. These results are consistent with the notion that anti-TNF effect of ABT-122 is the main driver of its efficacy, whereas the anti-IL-17A component does not significantly add anything to it in RA patients. Unless unproven, inhibition of the IL-17 pathway is poorly effective in RA.

Another molecule, whose effects on RA have been recently examined, is mavrimumab, a human mAb targeting granulocyte-macrophage colony-stimulating factor receptor  $\alpha$  (GM-CSFR $\alpha$ ). A phase IIb RCT (EARTH EXPLORER 2) has evaluated efficacy and safety of mavrimumab in RA patients with inadequate response to csDMARDs and/or TNFis except golimumab (GOL)(60). After randomisation, patients received mavrimumab 100 mg subcutaneously every other week or GOL, with background MTX. After 24 weeks of treatment, both mavrimumab and GOL were well tolerat-

ed but almost all the efficacy endpoints gave better results with GOL. However, mavrimumab demonstrated efficacy similar to GOL in the TNFis-IR subgroup. An analysis of available trials, which included also the aforementioned RCT, has assessed the long-term safety and efficacy in 442 RA patients receiving subcutaneous mavrimumab for a median of 2.5 years (61). These long-term data revealed that mavrimumab maintains a sustained efficacy over time, with 65% of patients achieving a DAS28-LDA and 40% achieving remission at week 122. Mavrimumab confirmed to have a good safety profile, with most common AEs, like nasopharyngitis and bronchitis, mild in severity. Other molecules have shown promising results. Denosumab, a fully human monoclonal antibody that binds to receptor activator of nuclear factor kappa  $\beta$  ligand (RANKL), leading to inhibition of osteoclasts in order to suppress bone resorption, was administered to 70 women with RA (on treatment) to evaluate the effects on joint destruction, assessing changes in modified total Sharp score (mTSS), erosions and joint space narrowing score at 12 months (62). After two administrations of denosumab, the authors have found a significant decrease in the values of mTSS (1.13 vs. 0.59,  $p=0.002$ ) and erosion scores (0.40 vs. 0.07,  $p<0.001$ ), whereas joint space narrowing score displayed a tendency to decrease (0.73 vs. 0.51,  $p=0.052$ ). These findings suggest that add-on denosumab treatment, in addition to the effect on osteoporosis, might suppress (or decelerate) joint destruction in RA patients.

#### Treatment strategies in particular clinical settings

Biological treatment availability has completely changed perspectives in the management of RA. However, the decision of bDMARDs initiation is clearly connected with intimal reasons regarding the best global strategy to adopt. Implementation of treat-to-target (T2T) strategies, from the beginning of the management of RA in its early phases, has been associated with relevant improving in numbers of outcomes, but the application and adher-

ence to T2T is not fully complete in daily clinical practice. In a recent analysis of the TRACTION trial, a randomised controlled clinical study investigating the effect of Learning Collaborative in implementation of T2T strategies, Zak and colleagues (63) have analysed the relevant barriers to T2T adoption. Among 90 barriers to treatment adjustment described, the main cause for non-selecting T2T was patients' preference (37.1% of the visits), followed by elevated disease activity score not reflective of RA disease activity (38.6%). These barriers, obtained in the context of a clinical trial specifically drawn to implement T2T application, are helpful in understanding how much they might count in clinical settings out of RCTs. In addition, the benefit of T2T approaches has been linked not only to prevention of radiographic progression, but also to partial repair of pre-existing bone erosions. In the work by Yue *et al.* (64), the authors have performed an open-label clinical trial comparing patients with early RA randomised to two different treatment strategies, aiming at ACR/EULAR remission ( $SDAI\leq 3.3$ ) or DAS28-CRP remission ( $DAS28-CRP<2.6$ ). High-resolution peripheral quantitative CT (HR-pQCT) was performed at baseline and after one year at second metacarpal head of the non-dominant hand. Among 63 patients, 36 erosions in each group were detected at baseline. Both treatment strategies resulted in similar radiographic outcomes, but achieving sustained SDAI remission resulted in higher erosions repair on multivariate logistic regression analysis after 12 months.

The adoption of bDMARDs is recommended in combination with csDMARDs, but biological (and tsDMARD) monotherapy occurs in approximately one third of cases in clinical practice. Emery and co-workers (65) have performed a SLR of RCTs including b/tsDMARDs as monotherapy, with the primary aim to assess efficacy of b/tsDMARDs when adopted as monotherapies. b/tsDMARDs monotherapy was globally more efficacious than placebo or csDMARDs monotherapy, and this was irrespective of the mechanism of action. However, more meaningful

efficacy outcomes were reached using combination regimens, and comparisons between monotherapy and combination regimens, in csDMARDs-IR, displayed higher efficacy for ETA combination therapy than ETA monotherapy, and not-inferiority for TCZ monotherapy than TCZ combination with csDMARDs. These results reinforce the need for utilisation of csDMARDs co-treatment in patients receiving b/tsDMARDs therapy; however, in some cases, monotherapy could be a reasonable and efficacious option.

The choice of the bDMARD to adopt after the failure of first biological agent is another critical point. Due to historical availability of TNFi, most of the patients have started their first-line bDMARD treatment strategy with one of the five TNFi. Current treatment recommendations are cautious regarding the best mechanism of action to choose at the failure of first-line TNFi, with switching to another TNFi opposed to the possibility of swapping to drugs with different mechanisms of action. Brown and colleagues (66) have recently performed a multicentre, phase III, open-label, parallel-group, three-arm, non-inferiority RCT (SWITCH trial) comparing the clinical endpoints and cost-effectiveness of alternative TNFi or ABA with RTX (with background MTX therapy), at the failure of first-line TNFi plus MTX therapy due to inefficacy. The primary outcome was reduction in DAS28 at 24 weeks. The study was interrupted earlier than expected due to recruitment issues, with 122 patients randomised to TNFi (n=41), ABA (n=41), or RTX (n=40). Alternative TNFi was shown to be non-inferior to RTX only in the intention-to-treat but not in the per-protocol population, while ABA was not demonstrated non-inferior to RTX. Despite early interruption, switching to another TNFi seemed more cost-effective than swapping to RTX or ABA. The issue of second-line treatment strategy has been addressed even in real-life settings. Gottenberg and colleagues (67) have performed an analysis of three French registries (AIR, ORA, and REGATE), investigating RA patients treated with RTX, ABA and TCZ (all drugs in IV formula-

tions). Main objective of the study was to compare effectiveness and safety of these different bDMARDs, the primary outcome was measured using treatment retention without failure at 24 months, and most of patients enrolled in the study were on treatment lines different from first-line. In the full analysis, 3,162 patients were included (1,614 RTX, 610 ABA, 938 TCZ). Drug retention rate was better in patients treated with RTX or TCZ than in those treated with ABA, with the study drug discontinued before month 24 in about 30% of those using RTX or TCZ and in 60% of those using ABA. Safety outcomes were comparable across groups.

Given overall costs and potential side effects of bDMARDs, a large body of literature, as already explained, is investigating the best modality to reduce doses or space administrations after achieving good clinical responses. Henaux *et al.* (68) have performed a SLR and meta-analysis of controlled trials, comparing bDMARDs discontinuation and tapering (dose reduction or spacing) *versus* continuation in RA patients in remission or LDA. The main objective of the meta-analysis was to assess the RR of losing remission or LDA and the risk of radiographic progression after (i) discontinuing or (ii) tapering doses of bDMARDs *versus* continuing the initial treatment. Among 9 trials comparing bDMARDs discontinuation *versus* continuation, the meta-analysis has showed an increased risk of losing remission (RR 1.97, 95%CI 1.43–2.73) or LDA (RR 2.24, 95%CI 1.52–3.30) and an increased risk of radiographic progression at 12 months (RR 1.09, 95%CI 1.02–1.17) when bDMARDs were discontinued. Among 11 trials comparing bDMARDs tapering *versus* continuation, there was an increased risk of losing remission (RR 1.23, 95%CI 1.06–1.42) in the tapering-group, while the risk of losing LDA (RR 1.02, 95%CI 0.85–1.23) and that of radiographic progression at 6–18 months (RR 1.09, 95%CI 0.94–1.26) were not significantly incremented. The results of this meta-analysis underline that bDMARDs tapering is a feasible and reasonable measure to adopt in patients reaching remission or LDA with bDMARDs.

### Non-targeted therapies: csDMARDs, NSAIDs, GCs, non-pharmacological treatment

The adoption of csDMARDs is part of first-line recommended treatment strategy in the management of RA patients and MTX is an essential part of this initial treatment. However, the best administration route of MTX and the role of other csDMARDs in combination with MTX are still matters of debate. Dhaon and co-workers (69) have performed a prospective monocentric study with the primary objective to compare low disease activity achievement at 24 weeks among different treatment modalities of MTX administration in a cohort of RA patients. They included 135 RA patients with moderate disease activity despite MTX 7.5 mg weekly. Patients were divided in 3 groups. Group I received MTX 7.5 mg in two or three different oral administrations per week, group II was treated with MTX 15 or 22.5 mg weekly in one single oral administration, and group III received MTX 15 or 22.5 mg weekly in a single parenteral administration. After 24 weeks, LDA achievement was similar across groups, while a significantly higher number of patients achieved SDAI remission in group I and group III with respect to group II, suggesting higher efficacy for split oral administration compared to single weekly oral administration, and a similar efficacy profile with respect to parenteral administration. This study, despite the limitations, might help in selecting an alternative treatment strategy in patients who are responsive to parenteral MTX but who enhance signs of poor tolerance. Regarding the role of other csDMARDs in combination with MTX, a work by Schapink *et al.* (70) has focused on the effect of hydroxychloroquine (HCQ) co-therapy in the management of early RA. In their observational analysis of a prospective Early RA cohort, the authors compared patients starting either MTX (25 mg/week) monotherapy (n=79) or MTX-HCQ (400 mg/day) combination (n=246) as first csDMARD treatment strategy. After 6 months, the improvement in DAS28-CRP was higher in the group receiving combination therapy, while, at 12 months, the improvement

became comparable, maybe due to efforts for intensifying treatment in the MTX monotherapy group. This study corroborates the role of csDMARD combination therapy in the management of RA. In line with this, a retrospective analysis of administrative healthcare databases (AHDs) of Lombardy region, Italy, highlighted that the combination of multiple csDMARDs with first-line bDMARDs resulted in reducing the risk of biologic withdrawal (HR 0.77, 95%CI 0.68–0.87), reflecting the role of csDMARDs co-therapy in increasing effectiveness and survival of concomitant bDMARDs (46).

Another important aspect to consider in RA management refers to GC therapy, despite a definition of standardised dosages to adopt in different clinical settings still lacks. A recent work, analysing 403 early RA patients from the ESPOIR inception cohort (71), has suggested that high and recent doses of GCs associated with radiographic progression at 5 years and the risk increased with the doses. Conversely, this association was lost when considering wider temporal windows (more than 6 months). These findings suggest aspects that need to be weighted when facing GCs administration to RA patients, but some possible explanations need to be considered, in particular recent high-dose GC treatment might have been reserved to elderly or comorbid patients with more severe disease and contraindications to other DMARDs, or to patients with recent disease progression (confounding by indication).

Apart from csDMARDs and GCs, NSAIDs are useful in alleviating inflammation and pain symptoms in RA patients, but are burdened by relevant side effects. Selective cyclo-oxygenase 2 (COX-2) inhibitors demonstrated an important risk of CV events. Solomon and colleagues (72) have performed an analysis of the PRECISION trial, a non-inferiority randomised, double-blind, active drug-controlled trial, with >24,000 patients ultimately enrolled, designed to assess the risk of CV events associated with celecoxib compared with the risk associated with commonly used s ibuprofen and naproxen. Patients with osteoarthritis (OA) and RA with

moderate basal CV risk were enrolled. After randomisation, RA patients received celecoxib, ibuprofen, naproxen or placebo. Among 2,436 RA patients, the risk of a major adverse CV event did not differ significantly between those randomised to receive celecoxib and those randomised to receive naproxen or ibuprofen. Even for other safety outcomes, celecoxib was not significantly associated with adverse events compared to other NSAIDs, while patients receiving celecoxib had a significantly lower overall mortality risk with respect to naproxen-treated subjects (HR 0.47, 95%CI 0.25–0.88). These findings, similar to what observed in OA patients, are reassuring regarding the use of COX-2 inhibitors at moderate dosages.

Apart from targeted and non-targeted drugs, the management of RA necessitates the adoption of numbers of non-pharmacological treatments. Selective exercises are crucial parts of them, aimed at improving mobility, strength, and functional ability. A recent SLR (73) of controlled clinical trials, published until July 2017, has investigated efficacy and safety profiles of hand exercise in patients with RA. A minimal benefit on hand function was demonstrated at medium and long term, with low effect on pain and no information regarding efficacy (ACR50 response). By the way, adherence to treatment was good (when adherence strategies were applied), and safety profile was acceptable. The overall quality of studies retrieved was highly variable (judged from very low-to-high), claiming for further researches with higher quality in conducting and reporting, and for development of a core set of outcome measures for conservative exercise in RA patients.

#### **Personalised and predictive treatment approaches: feasibility and innovation**

Current recommended treatment approach in the management of RA is based on ‘heuristic’ decisions, on “trial and error” basis. The possibility of personalising treatment, with stratification based on particular features of the disease or on available biomarkers, is not

fully defined, and many authors in recent years have searched for strategies aiming at identifying how to select the most effective treatment for each individual patient, without clear or univocal answers.

Among candidate biomarkers of response to different drugs, genetic biomarkers could help in predicting response to first-line treatment strategies, in particular MTX and TNFis, with the objective to reserve alternative therapies, at an earlier stage, to patients that would be refractory. Taking advantage from two large consortia using blood-based biomarkers and pathobiology to inform the stratification of all stages of RA treatment (the international Pharmacogenomics of Methotrexate in RA (PAMERA) and the UK Maximising Therapeutic Utility in RA (MATURA) consortia), Taylor and colleagues (74) have performed a genome-wide association (GWA) study of response to MTX monotherapy in early RA patients of European ethnicity. 1,424 patients were included, and GWA studies were performed using four separate analyses. However, no single nucleotide polymorphism (SNP) showed significant association with response to MTX at 3 to 6 months. Alternatively, López-Rodríguez and co-workers (75) have performed a benefit-cost analysis of a clinical-pharmacogenetics model for predicting response to MTX (CP-MTX). In this model, four clinical variables (disease activity, sex, RF and smoking status) and four SNPs (rs2236225, rs17602729, rs1127354, and rs2372536) in genes of the folate pathway were included. 720 RA patients receiving MTX monotherapy (mostly csDMARDs naïve) were enrolled, and predictive models were set up in order to identify patients that did not reach LDA at 6 months on MTX monotherapy. Analysing genetic components of the score, none of the four genotypes showed a significant correlation with response to MTX, while refractory subjects were more frequently women and with higher baseline disease activity. Using the CP-MTX model as a whole resulted in 79.7% positive predictive value (PPV) of identifying refractory patients, with 33.3% of pa-

tients that would have benefited from the application of the model (receiving an alternative treatment) and only 8.5% over-treated.

Even regarding TNFis treatment, there are problems in defining genetic biomarkers of response, and independent validation of potential candidates is needed, even when they reach the GWA level of significance. A validation study of 18 candidate SNPs that were previously associated with response to TNFis in RA has demonstrated, in 581 bDMARD naïve patients, that none of them was able to predict response at 3, 6 and 12 months (76). The possibility of integrating different SNPs in univocal models has been investigated by Canet and colleagues (77). The authors have performed a study in 548 RA patients treated with TNFis (discovery population), with the aim to investigate if 47 potentially functional SNPs in 16 steroid hormone-related genes were associated with response to TNFis. Afterwards, a replication sub-study was performed in 882 patients from the DREAM registry and 555 from the DANBIO. Finally, results from the two sub-studies were meta-analysed. After meta-analysis, carriers of the CYP3A4rs11773597C allele had a significantly larger decrease in DAS28 after the treatment with TNFis compared with patients carrying the GG genotype, while CYP2C9rs1799853T carriers associated with worse treatment response. Moreover, the authors included all the genetic polymorphisms associated with response to TNFis inside a model comprising age, sex, and RF. This model, when compared with a reference model including only demographic and clinical variables, allowed a 7%-higher detection of patients responsive to TNFis, underlining the importance of considering polymorphisms in steroid hormone-related genes in the building of predictive models of response to treatment, but highlighting, as well, the need for further research in the field.

Apart from genetics, cellular biomarkers, obtained from blood, synovial fluid (SF), or synovial membrane, are attractive in view of determining *a priori* (or in an early “window” of treatment) possible responses to treatment. A recent

Argentinian group of researchers (78) has focused on the role of inhibitory receptor expression on peripheral T-cells obtained from blood and SF in RA patients. Inhibitory receptors (*e.g.* CD160, PD-1, BTLA, and TIM-3) are important during initial phases of T-cells development, and play a role in “T-cells exhaustion”, a terminal-differentiation condition characterised by poor functionality. Among 51 patients, the presence of active T-cells (measured by CD68 expression) in peripheral blood correlated with expression of inhibitory receptors, suggesting that T-cells activation can induce inhibitory receptors. Contrariwise, when analysing low-functionally activated T-cells (CD68-low) in DMARDs-naïve patients with active disease, a lower percentage of CD8-positive cells expressing all 4 inhibitory receptors tested (CD160, PD-1, BTLA, and TIM-3) was demonstrated, with respect to treated-patients. Clinically, responders exhibited an increase in the frequency of CD68-low CD8<sup>+</sup> T-cells expressing CD160 or PD-1 (or both) after 3 months of treatment in comparison to baseline, while not-responders did not. These data suggest different roles of inhibitory receptors, connected with T-cells pro-inflammatory activation, but also with terminal effector memory differentiation, and the variation of less functional T-cells expressing these receptors might be able to guide treatment decisions.

Given their easier way of obtainment compared with other biomarkers, biomarkers from serum are among most-well studied biomarkers in RA, however large heterogeneity across studies has given, until now, few practical insights from a clinical perspective. The multi-biomarker disease activity (MBDA) score exploits the measure of 12 different serum proteins to assess RA disease activity, and it has been validated as connected to response to treatment and radiographic progression. Brahe *et al.* (79) have performed a *post hoc* analysis of OPERA double-blinded RCT, including 180 DMARDs-naïve early RA patients randomised to MTX plus ADA (n=89) or MTX monotherapy (n=91). The main finding of the work was the demonstration that

baseline MBDA was not able to predict response to treatment at 6 months (OR 1.01, 95%CI 0.99–1.03), while variation in MBDA score between baseline and 3 months was, at least partially (OR per unit of increase 0.98, 95%CI 0.96–1.00). Similarly, Roodenrijs *et al.* (80), in the analysis of three prospective cohorts of refractory RA patients, have demonstrated, for the first time, a correlation between variation in MBDA score (from baseline to month 6) and EULAR response to RTX (adjusted OR: 0.89, 95%CI 0.81–0.98).

These results, along with others not covered in this review, are promising in view of the possible integration of biomarkers in the clinical work-up for RA treatment stratification. In addition, they will help in understanding deep pathogenic processes and relationships among different immune-pathways crucial for synovial and systemic pathology.

### Extra-articular morbidity

#### Cardiovascular risk

Assessment and minimisation of CV risk in RA is one of the major challenges in the long-term management. Novel evidence reinforce the need of controlling disease activity and intensively treating traditional CV risk factors (81). A pooled analysis of RCTs data on baricitinib included 1,963 patients on baricitinib 2–4 mg/day, 330 on ADA and 1,558 on placebo, assessing variation of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride levels (82). Despite a significant variation in total cholesterol, the increase of HDL oversized the increase on LDL, leading to a not significant change in the LDL-C:HDL-C ratio from baseline to week 12 (placebo= -0.02, baricitinib 2 mg= -0.03, baricitinib 4 mg= -0.02) or week 24 (placebo= -0.03, baricitinib 2 mg= -0.04, baricitinib 4 mg= -0.01). After the initial increase from baseline to week 12, in patients receiving baricitinib 4 mg, LDL-C and HDL-C remained stable through week 104. The use of statins did not differently influence lipid profile in patients on placebo, ADA or baricitinib 4mg/day. These results support no major increase on the estimated CV risk according to

the Framingham risk score, and even a reduction of the risk using other prediction models. Data on CV events should confirm CV safety of baricitinib beyond CV risk estimations.

A meta-analysis of 11 observational studies has comparatively evaluated the risk of major CV events (MACE) of patient on bDMARDs (103,051 patients) and csDMARDs (83). The main analyses demonstrated a marginal risk reduction of MACE for TCZ *vs.* TNFis (pooled OR 0.59, 95%CI 0.34–1.00) but not for ABA (OR 0.89, 95%CI 0.71–1.11). However, the relative decrease of MACE in non-TNFis *vs.* TNFis was still statistically significant only in patients with prior coronary artery disease (CAD) (6 studies; OR 0.73, 95%CI 0.57–0.93), but not in patients without history of CAD (one study; OR 0.99, 95%CI 0.85–1.15). Another observational study on AHDs, compared the incidence of heart failure (HF) in 1,690 patients on ETA and 837 on ABA treatment (84). After adjusting for potential confounders, compared with ETA, ABA was not associated with a significant increase of hospitalisation for HF (HR 1.42, 95%CI 0.59–3.45). Exposure to csDMARDs was associated with an increased risk of MACE, as compared to treatment with TNFis (OR 1.58, 95%CI 1.16–2.15, I<sup>2</sup>=16%), both in cohorts where MTX was included (OR 1.45, 95%CI 1.09–1.93), or not (OR 2.57, 95%CI 1.32–5.00)(83).

Despite the limited disease-modifying role of HCQ, a potential role in CV risk management is suggested by observational studies. An AHD study included 173 HCQ-users and propensity score matched 173 non-users, evaluating incidence of CAD. HCQ-users showed a significantly lower risk of CAD (HR 0.32, 95%CI 0.18–0.56) (85). Another retrospective cohort study compared the occurrence of CV events in 241 HCQ-treated and 273 non-treated patients (86). HCQ treatment had an independent protective effect for all CV events (HR 0.46, 95%CI 0.29–0.73), though such association was particularly significant for higher HCQ daily dose (400 mg) users.

Beyond specific DMARDs treatment, treatment strategies may influence the

CV risk in RA patients. A 12-month open label randomised controlled trial enrolled 120 patients with recent-onset seropositive RA and compared 2 different T2T strategies, aiming at remission, on arterial stiffness (87). All patients were on treatment with intensive strategies, the SDAI-T2T group used SDAI  $\leq 3.3$  as target and early bDMARD in more severe patients, while a DAS28-T2T group used DAS28-CRP  $< 2.6$  as target and MTX as starting therapy for each patient. The study did not find significant differences in arterial stiffness measurements in SDAI T2T *versus* DAS28-T2T, and in clinical outcomes. A *post-hoc* analysis explored the presence of predictors of arterial stiffness improvement, identifying significant improvement of arterial stiffness in patients undergoing sustained remission regardless of the treatment strategy.

An open-label, randomised-controlled trial, including 320 patients with RA aged  $< 70$  years without prior CVD or diabetes mellitus were randomised 1:1 to either a treat-to-target approach or usual care of traditional CVD risk factors (88). The primary outcome was defined as change in carotid intima media thickness (cIMT) over 5 years, and the secondary outcome was a composite of first occurrence of fatal and non-fatal cardiovascular events. Out of the 320 randomised patients, 219 patients (68.4%) completed 5 years of follow-up, with a significantly reduction of the mean cIMT progression in the treat-to-target group compared with usual care (0.023 [95% CI 0.011–0.036] mm *vs.* 0.045 [95% CI 0.030–0.059] mm;  $p=0.028$ ). Cardiovascular events occurred in 2 patients (1.3%) in the treat-to-target group *vs.* 7 (4.7%) receiving usual care ( $p=0.048$  by log-rank test). These results support the efficacy of an intensive treatment of CV risk factors in RA.

Despite the relevance of disease activity control and traditional risk factors assessment is well established in RA, the implementation of such standard of care is still a major public health issue. A Dutch project tested an integrated rate care programme of CV screening and management of RA patients at population level (89). Primary and secondary care including primary care physicians

(PCP), rheumatologists and cardiologists set up a collaborative care process based on data sharing for patients' identification, active screening, CV risk stratification and individualised care plan (pharmacologic and non-pharmacologic) including annual based-follow-up. An analysis of the impact on quality of care of this programme, on 628 patients, has showed high CV risk screening rates, up to 88%, suggesting that population programmes are needed to fully translate evidence into practice.

#### *Infectious risk and vaccinations*

Due to well-known increased disease- and treatment-associated risks of infections in RA patients, vaccinations are one of the most important interventions to limit the disease burden. Several studies have investigated the immune responses to various vaccines in RA patients. A SLR and meta-analysis assessed the impact of MTX and b/tsDMARDs on immunogenicity of influenza (7 studies) and pneumococcal vaccines (2 studies)(90). Influenza vaccine responses to all subunit strains (H1N1, H3N2, B strain) were not significantly reduced in MTX- and TNFis-exposed RA patients, while MTX- (but not TNFis-) exposure was associated with reduced 6B and 23F serotype pneumococcal vaccine responses (RR 0.42, 95%CI 0.28–0.63, *vs.* 0.98, 95%CI 0.58–1.67). As a remark, combination of MTX with TCZ or tofacitinib was associated with reduced pneumococcal and influenza vaccine responses.

A parallel-group RCT has evaluated the effect of a 2-week interruption of MTX in RA patients on stable-dose MTX in terms of seroconversion and sero-protection of quadrivalent seasonal influenza vaccine containing H1N1, H3N2, B-Yamagata and B-Victoria (91). More patients who interrupted MTX for 2 weeks achieved satisfactory vaccines response than the group continuing MTX (75.5% *vs.* 54.5%,  $p<0.001$ ). Similar results were found in terms of sero-protection rates, with significant differences ranging from 10.7% to 15.9%, without changes in disease activity between groups.

Though immune response is a critical intermediate to ensure prevention of

infection, only few studies have specifically addressed clinical effectiveness of vaccinations (92). Among 3,748 RA patients (AHD study) who received influenza vaccination, matched with RA patients who did not received this vaccination (93), the overall risk of hospitalisation for septicaemia, bacteraemia or viraemia was significantly lower in vaccinated RA patients (HR 0.65, 95%CI 0.45–0.94), particularly in patients over 65 years (HR 0.56, 95%CI 0.36–0.89). Similar results were found for the risk of overall mortality (HR 0.62, 95%CI 0.39–0.97 in the overall group and HR 0.51, 95%CI 0.30–0.87 in patients with >65 years).

Despite accumulating evidence on efficacy and safety of vaccinations in RA, and consistent national and international recommendations, the translation of guidelines into practice is far from being achieved (92). A single arm interventional study has recently evaluated the impact of a multimodal intervention, consisting of an education session, electronic medical record alerts, and weekly e-mail reminders to health-care providers on missed opportunity to vaccination of RA patients (94). Such intervention led to an increased vaccine uptake in the 228 enrolled RA patients, from a 47% pre-intervention frequency of any missed opportunities for influenza vaccination to 23% post-intervention ( $p < 0.001$ ). Some barriers to vaccination in the pre-intervention phase, such as younger age, less frequent office visits, higher ESR, and negative attitudes about vaccines, were no longer associated with non-vaccination after the intervention, while other characteristics, including socio-demographic characteristics and prior adverse reactions to vaccines, still associated with lower vaccines uptake.

### Conclusions

We have reviewed the main novelties in the treatment of RA, following relevant publications across the last year. Despite the huge amount of data accumulating around well-established targets, such as IL-6 and JAKs, and novel promising targets, in absence of robust treatment selection biomarkers, treatment strategies remain the cornerstone

of RA management, rather than specific drugs. Patient-centred and healthcare system outcomes are taking more importance in the evaluation of the value of interventions beyond simple efficacy demonstrated in clinical trials. Treating rheumatologists and patients are still waiting for the promise of personalised medicine in RA.

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